REMARKS

Status of Claims

Upon entry of this amendment, claims 11-12, 21-22, 25-30, 33, 35-37, 39-48 are pending in the instant application. Claim 12 has been amended solely to insert a comma to correct a typographical error. Accordingly, no new matter is added.

§103(a) Rejection

The Examiner has maintained the rejection of claims 11-12, 21-22, 25-30, 35-37, and new added claims 46-48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rice et al. J. Heterocyclic Chem., 10(5):731-735 (1973)(referred to hereinafter as "Rice") taken with Mirabelli et al. Anti-Cancer Drug Design, 3(4):231-242 (1989)(referred to hereinafter as "Mirabelli") in view of Badger et al. U.S. Patent No, 5,602,166 (referred to hereinafter as "Badger") and Dagger et al. U.S. Patent No. 5,939,450 (referred hereinafter as "Dagger") and says that Applicants' arguments are unpersuasive. Applicants submit that one of ordinary skill in the art would not combine the teachings of Rice, Mirabelli, Badger, and Dagger to reach the present invention with predictable results. Further, Applicants submit that the present invention provides secondary considerations, such as unexpected/superior properties that are not taught or suggested by the combination of Rice, Mirabelli, Badger, and Dagger. Applicants traverse.

Reasonable Expectation of Success:

The consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success, viewed in the light of the prior art. *In re Dow Chemical Co.*, 837 F.2d 469 (Fed. Cir. 1988). Evidence showing there was no reasonable expectation of success may support a conclusion of non-obviousness. *In re Rinehart*, 531 F.2d 1048, 189 USPQ 143 (CCPA 1976).

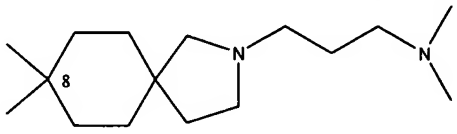
Applicants assert that the skilled artisan reading Rice in view of Mirabelli in view of Badger in view of Dagger would not arrive at the instant invention. Specifically, one of ordinary skill in the art would not have predicted that modification of the compounds taught in Rice

would lead to the dramatic and unexpected result of the instant invention, a method of treating a broad number of cancers by administering a compound having >5 carbon at the 8-position of the azaspirane ring.

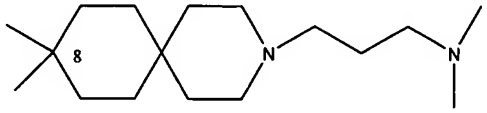
For clarity, Applicant is describing the teachings of Rice, Mirabelli, Badger, and Dagger individually, but are traversing the rejection with respect to the combination of these references, *infra*.

Rice

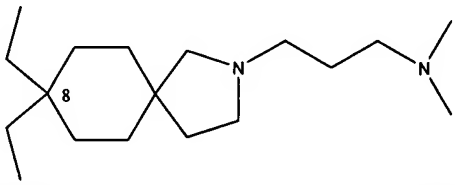
Rice merely teaches 4 compounds, which contain either two methyl substituents or two ethyl substituents at the 8-position of the azaspirane ring. The structures of these compounds and their names, as disclosed in the Rice abstract, are shown below:



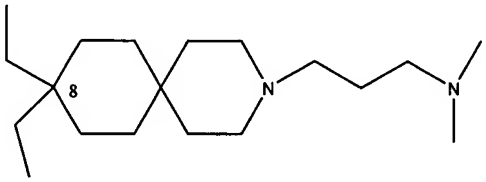
N-(2-Dimethylaminopropyl)-8,8-dimethyl-2-azaspiro[4,5] decane (**1**)



N-(3-dimethylaminopropyl)-9,9-dimethyl-3-azaspiro[5.5]undecane (**3**)

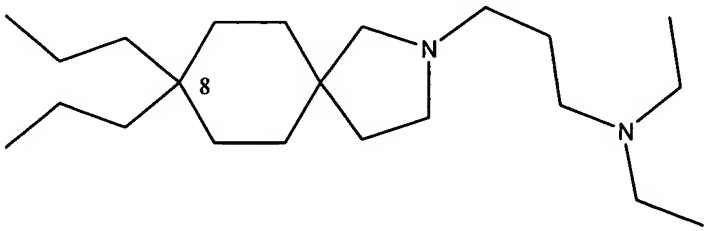


N-(2-Dimethylaminopropyl)-8,8-diethyl-2-azaspiro[4,5] decane (**2**)



N-(3-dimethylaminopropyl)-9,9-diethyl-3-azaspiro[5.5]undecane (**4**)

The Examiner states on page 5 of the Office Action that if the abstract of Rice cites a compound name that is different from that of instant claim 11, this needs to be explained. Accordingly, Applicants have shown above the four compounds as named in the Rice abstract and assert that these compounds are not the compound of instant claim 11. The compound of instant claim 11 is N,N-dimethyl-8,8-*dipropyl*-2-azaspiro[4,5]decane, a compound with two propyl substituents at the 8-position of the azaspirane ring:



Rice does not teach compounds with propyl substituents at the 8-position of the azaspirane ring. Thus, the statements by the Examiner on page 5 of the Office Action and on

page 6 of the previous Office Action, mailed June 14, 2007 that Rice teaches the drug N,N-dimethyl-8,8-*dipropyl*-2-azaspiro[4,5]decane are incorrect, because no azaspirane compounds containing a dipropyl substituent at 8-position are explicitly disclosed in Rice.

On page 3 of the Office Action, the Examiner says that Rice teaches that the replacement of a hydrogen atom with a one-carbon methyl group at the 8-position of the azaspirane ring increases the inhibitory effect five fold in human mammary cancer and suggests further substitutions. The Examiner goes on to say that based on Rice, the skilled artisan would have been motivated to explore other alkanes at that position to arrive at the claimed invention. Applicants respectfully disagree.

Applicants submit that Rice merely makes reference to a 1963 journal article, which describes replacing the hydrogen atom at the 8-position of the azaspirane ring with a methyl group to produce increased inhibition of a single type of cancer, human mammary cancer. There is no further detail provided in Rice related to a specific type of cancer. Regarding the four compounds actually prepared, Rice only provides a one sentence assertion that two of the four compounds disclosed kill cancer cells. No experimental details are provided related to testing the two compounds for mammary cancer or any other type of cancer. Testing for the other two compounds is said to be in progress.

Further, contrary to the Examiner's assertion that one of ordinary skill in the art would have been motivated to explore other alkanes at the 8-position, Rice contains no teachings which suggest that modification of the Rice compounds e.g., by extending the alkyl chain at the 8-position might lead to compounds which would be effective for treating a broad range of cancers. To the contrary, Rice reports no difference in the efficacy of compounds, which contain alkyl chains of different length at the 8-position. *See*, page 732, left column, paragraph 3 of Rice.

Therefore, Applicants submit that based on the very limited reference to a single type of cancer, in combination with results that show no significant difference in efficacy between compounds with alkyl chains of different lengths at the 8-position of the azaspirane ring, one of ordinary skill in the art would not have any basis to predict that modifying the compounds of Rice would lead to compounds effective in a broad range of cancers as claimed.

Mirabelli

Mirabelli does not cure the deficiencies of Rice. While the Examiner states that Mirabelli

was used to show that these azaspirane compounds are known to inhibit cancer and that the reference refers to prostate and mammary cancer in the teaching, Applicants respectfully disagree with these conclusions.

Mirabelli, similar to Rice, merely teaches compounds containing <5 carbon atoms at the 8-position of the azaspirane ring for the treatment of a single cancer (colon). Applicants submit Applicants submit that the skilled artisan would not conclude reading Mirabelli, alone or in view of Rice, that its azaspirane compounds containing <5 carbon atoms at the 8-position can be used to inhibit any and all types of cancer. More specifically, one of ordinary skill would not predict that modification of the Mirabelli compounds would lead to the claimed invention of a widely applicable method of treating the various, specific cancers as instantly claimed. Table II of Mirabelli provides the in vitro potency of spirogermanium analogs in a colony formation assay using HT-29 colon cancer cells. The two most potent compounds in the table have IC50 values in the high >10 μM range. For example, compound **8**, an azaspirane containing a 4-carbon t-butyl group at the 8-position has an IC50 value of 11μM and compound **2**, an azaspirane containing a 4-carbon t-butyl group at the 8-position has an IC50 value of 19 μM. In comparison, the claimed compounds are dramatically and unexpectedly more potent exhibiting anti-proliferative activity in the low micromolar range. *See*, e.g., the instant specification at Example 5, where using a compound of the claimed invention, the IC50 value against 5 colon cancer cell lines ranged from 0.26 μM - 1.3 μM and Example 1, where the proliferation of both CaCo-2 and T84 colon cancer cells was inhibited with IC50 values in the range of 0.625 and 1.25 μM. For a more direct comparison of the potency the claimed compounds with compounds having alkyl groups with fewer carbon atoms at the 8-position, Applicants direct the Examiner's attention to the instant application, Example 8, Table 7, where the percent inhibition of proliferation at 5μM of the claimed compounds against CaCo-2 cells was 73-86%, whereas compounds with <5 carbon atoms showed only between 0-45% inhibition.

The Examiner states that Mirabelli further teaches that increased cytotoxic potency within the group of carbon-containing analogs was directly related to increase in length in the alkyl group(s). However, Applicants submit that it is not clear that the teachings in Mirabelli fully support this statement. For example, the results in Table II show that compound **5**, having two methyl groups at the 8-position, is <u>less</u> potent than compound **4**, which only contains one methyl group and a hydrogen atom. Based on statement above that increased cytotoxic potency is

directed related the increase in length of the alkyl group, one would have expected the opposite result and for compound **5** to be more potent.

Applicants further submit that Mirabelli teaches away from the claimed invention which is directed to a broad range of cancers, based on the fact that none of the Mirabelli carbon-containing compounds, all with < 5 carbon atoms at the 8-position, demonstrated anti-tumor activity against leukemia. *See*, page 237, second paragraph of Mirabelli. Based on the fact that the Mirabelli compounds are not effective against leukemia, it would not have been obvious to the skilled artisan that modifying the Mirabelli compounds would lead to compounds effective across a broad range of cancers with predictable results. This includes the cancers, mammary adenocarcinoma and prostatic carcinoma, mentioned in the introductory remarks of Mirabelli relative to the metal-containing compound.

Badger

Badger does not cure the deficiencies of Rice and Mirabelli. The Examiner states that Badger teaches the compound and it is known that increasing the alkyl substituents makes the compound less toxic, and therefore one of ordinary skill in the art would have been motivated to combine the knowledge in the art, modify the compound of Rice and Mirabelli to the compound of Badger and use it in the treatment of breast cancer because cytokines have been found to play a major role in the control of estrogen in breast cancer e.g., Nakashatri has showed that cytokine II is responsible in majority of node positive breast cancer.

As discussed in detail above, Rice and Mirabelli are deficient because the skilled artisan would not predict that modification of the compounds of Rice and Mirabelli would predictably lead to the claimed invention of a method of effectively treating a wide range of cancers using a compound with >5 carbon atoms at the 8-position. Badger does not cure the deficiencies of Rice and Mirabelli, because Badger does not teach a method of treating a wide range of cancers using an azaspirane compound. Instead, Badger merely teaches a method of inhibiting cytokine production and lists at least 25 diseases/conditions which are exacerbated by IL-1 or TNF production and none of these 25 diseases/conditions are cancer.

The Examiner states on page 7 of the Office Action that cytokines have been found to play a major role in the control of estrogen in breast cancer and then makes reference to Nakashatri as an example showing that the cytokine IL-1*a* is responsible for the induction of NF-

kB activation in fibroblasts and the presence of IL-1 transcriptase in the majority of lymph node-positive breast cancer. The Examiner further suggests because Nakashatri has shown that cytokine II is involved in positive breast cancer, and because Badger teaches the compound is a cytokine inhibitor, the claimed invention is obvious. Applicants respectfully disagree with the Examiner's assertion that because cytokines have been shown to play a role in breast cancer then *any* cytokine inhibitor could therefore be used to treat cancer with predictable results. Nakshatri merely shows the presence of a cytokine transcript in breast tissue. Nakshatri has not shown any evidence that cytokine inhibition predictably results in the treatment of breast cancer. Further, Nakashatri does not show that cytokine inhibition predictably results in an effective treatment of a wide range of cancers as claimed in the present invention. Badger, even in view of Nakshatri, provides no motivation for the skilled artisan to test the compounds against cancer. As such, Applicants assert that one of ordinary skill in the art reading Badger in view of Rice and Mirabelli would not predict that azaspirane compounds which inhibit cytokine production would be useful for treating the broad range of claimed cancers.

Dagger

Dagger does not cure the deficiencies of Rice, Mirabelli, or Badger. Dagger merely teaches the dimaleate salt of the azaspirane compound, N,N-dimethyl-8,8-dipropyl-2-azaspiro[4,5]decane-2-propanamine and notes the compound is useful as an immunomodulatory agent, particularly in the treatment of rheumatoid arthritis. As such, Applicants assert that one of ordinary skill in the art would not predict that the compound of Dagger would be useful for the treatment of the claimed cancers.

Based on the foregoing, Applicants submit that the skilled artisan reading the combination of Rice, Mirabelli, Badger, and Dagger would not arrive at the instant invention with predictable results.

Secondary Considerations:

Moreover, a determination of whether the claimed subject matter as a whole would have been obvious at the time the invention was made also involves factual findings with respect to

secondary considerations, including long felt need in the art and superior/unexpected results. *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966).

The claimed invention is a method of treating ten different types of cancer by administering a compound with >5 carbon atoms at the 8-position of the azaspirane ring. Specifically, the instant specification shows that the compounds of the claimed invention inhibit proliferation and induce apoptosis in essentially all of the human cancer cell lines included in the NCI screening panel. *See*, Example 5, Tables 1a, 1b, and 2, which shows cytostatic effects against a panel of 60 human cancer cell comprising multiple human cancers and the results include complete inhibition of tumor cell growth. The compounds of the claimed invention are noted to be particularly potent on metastatic cells. Example 4 shows increases in activities of both caspase-3 and -9, thus confirming that the claimed compounds induce apoptosis via activation of these pro-apoptotic enzymes. The instant specification further shows that the compounds of the claimed invention are inhibitors of angiogenesis in a battery of HUVEC-based assays and in the developmental of angiogenesis CAM assay. *See*, Examples 2, 3, 6, 8, 9, 10, and 11. In particular, Example 11 shows the surprising effect of very potent inhibition of migration reaching complete inhibition. This result is of great importance since cell migration is an extremely complex process that plays a critical role in cancer invasion and metastatsis. Accordingly, the instant specification clearly demonstrates that the compounds used the claimed methods are tremendously effective anti-proliferative and anti-angiogenic agents which are broadly applicable in a number of different cancers.

Reconsideration and withdrawal are respectfully requested.

Double Patenting

Claims 11-12, 21-22, 25-30, 35-37 and 46-48 have been provisionally rejected on the basis of nonstatutory obviousness-type double patenting as being unpatentable over claim 111 of copending Application No. 10/548794. Applicants postpone the filing of a terminal disclaimer until the claims have otherwise reached allowance.

CONCLUSION

In view of the aforementioned remarks, the Applicants believe that each of pending claims is in condition for allowance. Reconsideration, withdrawal of the rejections, and passage of the case to issue is respectfully requested. A notice to this effect is earnestly solicited.

If, upon receipt and review of this amendment, the Examiner believes that the present application is not in condition for allowance and that changes can be suggested which would place the claims in allowable form, the Examiner is respectfully requested to call Applicants' undersigned counsel at the number provided below.

Respectfully submitted,

Dated: September 22, 2008

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